

Application No.: 09/421,971 Attorney Docket No.: SALK2350  
Filing Date: October 20, 1999 (088802-5351)  
Supplemental Response after Final (mailed 11/19/02, Paper No. 15) faxed September 4, 2003  
Page 6 of 9

### Remarks

Courtesies extended to Applicants' representatives during the telephonic interview held on September 3, 2003 are acknowledged with appreciation.

In accordance with the present invention, there are provided chimeric proteins comprising a covalent fusion of at least two functional protein units, wherein each functional protein unit comprises the dimerization domain of a member of the steroid/thyroid hormone nuclear receptor superfamily (see Figure A schematic below showing 2 functional protein units, each containing a dimerization domain, which are covalently fused into a single polypeptide molecule).

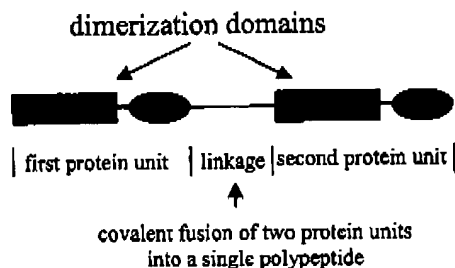


Figure A – exemplary chimeric fusion protein construct

Claims 1-11 and 13-22 remain pending pursuant to this communication. By this response, claim 1 has been amended to define Applicants' invention with greater particularity. This amendment adds no new matter and is fully supported by the specification and the original claims. Applicants respectfully submit that the amendment presented herein places the application in condition for allowance or, at a minimum, reduce the issues for appeal. Accordingly, entry of the amendment is respectfully requested. The present status of all claims in the application, and current amendments thereto, are provided in the listing of claims presented herein beginning on page 2.

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Supplemental Response after Final (mailed 11/19/02, Paper No. 15) faxed September 4, 2003  
Page 7 of 9

The rejection of claims 1-5, 14, 19 and 22 under 35 U.S.C. § 102(e), as allegedly being anticipated by U.S. Patent No. 5,830,462 to Crabtree *et al.* (hereinafter referred to as "the '462 patent"), is respectfully traversed. As discussed during the recent telephone interview, Applicants' invention clearly distinguishes over the '462 patent by requiring a chimeric protein comprising at least two functional protein units that are covalently fused to provide a single polypeptide capable of spontaneous dimerization either internally (endodimer) or with a dimer partner in various conformations (see, for example, specification at Figure 7). Indeed, as acknowledged by the Examiner, the claims are intended to "read on the use of a covalent linker to produce the single polypeptide" (see Advisory Action, Paper No. 21, at page 2).

Applicants respectfully submit that the '462 patent does not teach or suggest such a covalent linkage of two protein units. In contrast to the single polypeptide molecule contemplated by the present claims, the '462 patent teaches the association of two separate protein molecules via a ligand molecule (see, for example, Figure 14 of the '462 patent). Moreover, the '462 patent teaches ligand-induced dimerization, as opposed to a covalent fusion. Indeed, the Examiner acknowledges that proteins of the '462 patent undergo "ligand-mediated oligomerization" (see Office Action, Paper No. 15, at page 4, lines 6-7). The ligand of the '462 patent is defined in terms of its binding affinity, *i.e.*, the dissociation constant  $K_d$  between the ligand and the two-protein complex (see the '462 patent, at column 3, lines 24-30). By definition, the binding of such a ligand to the two-protein complex is a reversible process, for example, via hydrogen bonding, *etc.*, as opposed to a covalent fusion of two molecules to create a single molecule.

Therefore, the '462 patent does not teach or suggest the covalent fusion of at least two functional protein units to create a single chimeric protein. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 1-5, 14, 19 and 22 under 35 U.S.C. § 102(e).

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Supplemental Response after Final (mailed 11/19/02, Paper No. 15) faxed September 4, 2003  
Page 8 of 9

The rejection of claims 1-11, 13, 14 and 19-22 under 35 U.S.C. § 103(a), as allegedly being unpatentable over the '462 patent in view of U.S. Patent No. 6,265,173 to Evans *et al* (hereinafter referred to as "the '173 patent"), is respectfully traversed. Applicants respectfully submit that neither reference, either taken alone or in combination, teaches a single polypeptide unit comprising at least two covalently fused protein units.

As noted above, the '462 patent does not teach or suggest a chimeric protein comprising at least two protein units that are covalently fused. The '173 patent is unable to cure the deficiencies of this primary reference, because it also does not teach or suggest a single polypeptide unit. The '173 patent only contemplates multimeric species of a receptor member of the steroid/thyroid superfamily with an ultraspiracle receptor dimer partner, *i.e.*, the non-covalent association of two separate protein molecules. Thus, the multimeric species disclosed in the '173 patent are the result of the dimerization of two independent molecules, each containing one dimerization domain.

Therefore, the chimeric protein of the present invention cannot be rendered obvious by the cited references. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 1-11, 13, 14 and 19-22 under 35 U.S.C. § 103(a).

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Page 9 of 9

**Conclusion**

In view of the above amendments and remarks, prompt and favorable action on all claims is respectfully requested. In the event any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

Respectfully submitted,

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